Targeting More Than Pain: A Reflective Review on Drug Therapy for Knee and Hip Osteoarthritis

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***Abstract*—Osteoarthritis (OA) of the knee and hip is a leading cause of pain and disability worldwide [16,17]. Traditional pharmacotherapies, such as NSAIDs, acetaminophen, and intra-articular agents, offer symptomatic benefits but do not alter the disease trajectory [18-20]. Emerging disease modifying osteoarthritis drugs (DMOADs), such as NGF inhibitors (tanezumab, fasinumab), sprifermin (FGF-18), NLRP3 inflammasome inhibitors (e.g., DFV890), senolytics, protease inhibitors, and gene therapies targeting IL-1Ra are in clinical development [1-7,22-24]. While structural and symptomatic signals are encouraging, safety concerns (e.g., rapidly progressive OA), small trial size, and variable endpoints limit conclusions [14,22,24]. Precision medicine, through phenotype selection, digital biomarkers, and combination regimens, may be the key to successfully integrating next-generation therapies [7,24,25].**

I. INTRODUCTION

Osteoarthritis is now recognized as a whole-joint organ disease, involving cartilage loss, synovitis, subchondral bone changes, ligament and meniscal involvement, and neuroinflammatory pain pathways [16,17]. The burden of knee and hip OA is rising globally due to aging, obesity, and sedentary lifestyles [16,17]. In India, up to 22–28% of adults over 60 years have symptomatic knee OA, with high rates in postmenopausal women [8]. Standard symptomatic pharmacotherapies are inadequate for changing the structural progression [18–20]. Osteoarthritis (OA) is a complex and multifaceted condition that affects the entire joint structure, extending beyond the traditional view of cartilage degeneration [16,17]. This whole-joint organ disease encompasses a range of pathological changes, including synovial inflammation, alterations in subchondral bone, damage to ligaments and menisci, and the activation of neuro-inflammatory pain pathways [16,17,24]. The interplay between these various components contributes to the progressive nature of OA and the challenges in developing effective treatments [14,24]. The global prevalence of knee and hip OA is on the rise, driven by several factors including an aging population, increasing rates of obesity, and sedentary lifestyles [16,17]. This trend is particularly evident in countries like India, where up to 28% of adults over 60 years old experience symptomatic knee OA, with postmenopausal women being disproportionately affected [8]. The complex nature of OA, combined with its increasing prevalence, underscores the urgent need for more effective interventions [16,17,24]. Current pharmacological treatments primarily focus on symptom management and are inadequate in addressing the underlying structural progression of the disease, highlighting the need for novel therapeutic approaches that target the multiple aspects of OA pathology [18–20,24].

Pathophysiology Overview

Osteoarthritis (OA) pathology includes mechanical cartilage breakdown, dysregulated bone remodeling, synovial inflammation driven by NF-κB/JAK-STAT activation, and pain amplification via sensitization [16,17,24]. Cartilage deterioration occurs from enzymatic breakdown and mechanical stress, affecting the joint's cushioning and increasing friction [16,17,24]. Matrix metalloproteinases (MMPs) and aggrecanases mediate this breakdown, while dysregulated bone remodeling alters bone structure and stability, leading to changes like sclerosis and osteophyte formation [16,17,24]. Inflammation from the synovium produces proinflammatory mediators, exacerbating cartilage degradation and inducing a self-perpetuating damage cycle [16,17,24]. Peripheral and

central sensitization processes amplify pain, altering nociceptor sensitivity and chronic pain perceptions [15]. The development of Disease-Modifying Osteoarthritis Drugs (DMOADs) aims to target specific pathways in OA, potentially transforming treatment approaches by addressing underlying disease mechanisms [1–7,24].

II. ESTABLISHED PHARMACOTHERAPY

2.1 Topical and Oral NSAIDs

NSAIDs like ibuprofen, naproxen, diclofenac, and celecoxib lessen prostaglandin-mediated pain, while topical diclofenac (1% gel) provides local analgesia with very little systemic absorption, making it particularly appropriate for older individuals or those at risk for gastrointestinal or renal issues [10,18–20]. Oral NSAIDs, on the other hand, pose risks of cardiovascular events, renal damage, hypertension, and gastrointestinal bleeding [18–20]. COX-2 selective drugs, such as celecoxib, may have somewhat more favorable gastrointestinal profiles, but the cardiovascular risk remains [18–20].

Typical dosing:

- Ibuprofen: 400–600 mg three to four times daily
- Naproxen: 500 mg twice daily
- Diclofenac: 50–75 mg twice daily
- Celecoxib: 100–200 mg once or twice daily
- Topical diclofenac: up to 2 g daily for no more than two joints

NSAID hypersensitivity, heart failure, severe renal impairment, and active ulcers are contraindications [18–20]. Topical NSAIDs and paracetamol are advised in high-risk patients by guidelines like OARSI and EULAR [10,18,19].

2.2 Paracetamol (Acetaminophen)

It provides mild to moderate pain relief through the central COX and serotonergic pathways [9,18–20]. Doses range from 3 g/day to 2 g/day if the patient is elderly or has liver issues [18–20]. The effectiveness is only moderate, and there are no peripheral anti-inflammatory effects [18–20].

2.3 Tramadol and Opioids

Tramadol (50–100 mg every 6 hours, up to ~400 mg/day) is the most frequent medication used for refractory pain that does not respond to safer treatments [18–20]. The risks of tramadol include dependence, sedation, constipation, respiratory depression, and falls, which are particularly alarming for elderly people [18–20]. It is advised to use it for a short time with careful monitoring and supportive bowel regimens [18–20].

2.4 SNRIs (Duloxetine)

In patients with knee osteoarthritis (OA) who have features of central sensitization, low-dose duloxetine (30 mg increasing to 60 mg daily) has been demonstrated to be effective in reducing pain [9,18,19]. It affects the descending pain inhibition pathway [9,18,19]. Among the adverse effects are nausea, dry mouth, sleeplessness, and high blood pressure [9,18,19]. It is not recommended for individuals with hepatic illness or uncontrolled hypertension [18,19].

2.5 Corticosteroids Intra Articular

Knee joint injections (20–40 mg of triamcinolone or methylprednisolone) offer symptomatic alleviation for 4–8 weeks, while hip injections must be administered with imaging guidance [11,18,19]. Repeated injections (no more than 3–4 per year) run the risk of cartilage injury, momentary hyperglycemia in diabetics, and uncommon infection [11,18,19].2. 6 Hyaluronic Acid (HA) administered into the joint. Its goal is to lower friction and restore synovial fluid viscosity [18,20]. There is evidence that it causes a little improvement in pain and function in knee OA, but there is not much information available for hip OA [18,20]. They are often given as a single dose of high molecular weight medication or three to five weekly doses of low molecular weight medication [18,20]. Potential side effects include localized discomfort and, rarely, pseudosepsis [18,20]

III. INNOVATIVE AND EMERGING THERAPEUTICS (DMOADS)

3.1 NGF Inhibitors: Tanezumab and Fasinumab

Monoclonal antibodies that neutralize NGF target the pain sensitization pathways [6,22]. Meta-analyses have revealed significant WOMAC pain and functional improvements (SMD ~–2.2) [6,22]. Phase III data in knee and hip osteoarthritis have shown superiority over placebo, naproxen, and oxycodone, but about 1.3% of patients developed rapidly

progressive osteoarthritis (RPOA), particularly with higher doses and NSAID coadministration [6,22]. Intensive safety monitoring led to the lifting of regulatory holds [22]. Typical dosage: 2–5 mg administered subcutaneously at baseline and week 8 [6,22].

3. 2 Sprifermin (rhFGF-18)

FGF-18 promotes chondrocyte proliferation through the FGFR3c [13,24]. The forward trial's five-year data demonstrated that the high-dose group had a dose-dependent rise in cartilage thickness and 0% progression to total knee replacement, compared to around 10% in the high-risk placebo subgroup [13]. In the overall cohort, there was a modest symptomatic WOMAC benefit, but there was a substantial benefit in a "subgroup at risk" (baseline moderate pain + narrow joint space) [13]. The safety profile was favorable, with mostly mild injection site reactions, and the structural benefit was maintained with periodic injections (every 6–12 months) [13].

3. 3 Inhibitors of the NLRP3 Inflammasome: DFV890

DFV890 is an oral small-molecule inhibitor that targets NLRP3 to reduce IL-1β and IL-18-mediated inflammation [24]. A 2024 phase Ib/IIa trial evaluated twicedaily dosing (10 mg, 25 mg) in symptomatic knee OA, with KOOS improvement endpoints [24]. The efficacy data are awaiting publication, and the safety data are encouraging [24]. It represents a first-in-class, orally available anti-inflammatory DMOAD [24].

3. 4 Agents targeting the Wnt pathway, senolytics, and protease inhibitors

Many substances aimed at cartilage breakdown and joint signaling are being researched for osteoarthritis (OA) [2,12,23,24]. MIV 711 demonstrated slight symptom relief even with structural advantages [1]. GLPG1972 showed cartilage preservation but inconsistent pain alleviation [2]. Lorecivivint provided structural benefits in certain subgroups, whereas senolytic UBX0101 did not enhance symptoms, emphasizing persistent difficulties in OA management [2,23].

3. 5 Methods of Gene Therapy

AAV vectors are being evaluated in humans for gene delivery of IL-1Ra [3,4]. In the phase I data (n=9), there was persistent transgene expression, pain, and functional enhancement without any significant adverse effects [3]. The main difficulties include the scalability of production, durability, cell retention in shear environments, and vector immunogenicity [4].

3. 6 Biomechanical and Regenerative Biologicals

While hip and knee osteoarthritis have comparable pathologies, treatment methods vary because of anatomical differences, available evidence, and clinical considerations [16,17,24]. Knee injections are straightforward and frequent, whereas hip injections are more complicated, needing imaging and carrying higher risks [11,18]. Most DMOAD studies concentrate on knee OA, resulting in scarce data on hip OA [13,24]. Hip OA can also manifest as pain in the groin or thigh, influencing medication response and delivery [16,17]. Hip replacements are typically performed sooner because of their significant functional impact, while knee OA provides a more extended period for the effectiveness of DMOADs [16,17]. These variations affect the appropriateness and timing of injectable or regenerative therapies [16,17,24].

IV. PATIENT STRATIFICATION, DOSAGE, AND SAFETY

- Old Comorbidity and: Use topical therapies or the lowest effective dose of NSAIDs if at all possible. Avoid NSAIDs if the eGFR is below 30 mL/min. Renal/Hepatic Dysfunction [18,19,20].
- Avoid using acetaminophen in dosages exceeding 2 grams daily, keep a close watch on how your body processes duloxetine, and steer clear of any medications that lack data on how they may harm your kidneys. Condition of the cardiovascular system [9,18,19].
- Be careful while using systemic NSAIDs and avoid COX2 inhibitors in those with a history of stroke or myocardial infarction. Diabetes/corticosteroids [18,19,20].
- With IA steroids, monitor your blood glucose levels and use them judiciously [11].
- Gene therapy is still in the experimental stage; NGF inhibitors require close monitoring for RPOA and prior treatment imaging; Sprifermin appears to be well tolerated but may require several doses [6,13,22].

- Precision medicine is necessary to identify phenotypes, such as inflammatory dominant versus cartilage loss dominant, central sensitization, imaging biomarkers, and the alignment of treatment choices accordingly [7,24,25].

V. HYPOTHETICAL INDIAN CLINICAL VIGNETTES

Case 1 : Linda's Story: Fighting Knee Pain with Hope and a Little Help from Science

"I never thought a little joint pain would change my life so much," says Linda, a 67-year-old retired schoolteacher with a love for gardening and quiet morning walks. For years, her knees had whispered discomfort just a dull ache here and there. But gradually, those whispers turned into something louder, something that made her think twice before walking down to her favorite bench by the lake or kneeling to plant her beloved lavender bushes.

She was diagnosed with moderate knee osteoarthritis, and on top of that, she already had high blood pressure and stage 3 chronic kidney disease. "It was a tricky situation. I couldn't just pop a painkiller and move on," she recalls. So, her doctor started her on topical diclofenac. "It helped, but only a little it was like putting a band-aid on something deeper."

The nights were the worst. "I'd toss and turn, trying to find a position that didn't make my knee throb. Some nights I'd just get up and sit by the window till morning." Eventually, her physician introduced duloxetine. Starting with 30 mg and then moving up to 60, it not only took the edge off the pain but also gave her back the gift of sleep. "I finally slept through the night after what felt like forever. That alone made me feel human again."

An MRI confirmed what they suspected thinning cartilage in her knee. When her doctor mentioned a clinical trial for sprifermin, a drug that might help grow cartilage back, she was hesitant. "I was skeptical at first. I thought, 'At my age? Regrowing cartilage? Sounds like science fiction.' But I didn't want to keep losing pieces of my life to pain, so I signed up."

She began receiving injections every six months. The results didn't happen overnight, but follow-up scans told a new story: her cartilage was actually thickening. "It was like watching a fading photo come back into focus," she says with a smile. Pain wise, things stayed pretty steady around a 3 or 4 out of 10 but that stability meant everything. "I could walk down to the park again, tend to my garden without wincing, and even chase my grandson a little in the yard. I hadn't done that in years."

Best of all, she hasn't experienced any side effects. "That's the part I'm most grateful for. At my age, you start to expect trade-offs with every new treatment. But this time, it's just been progress."

Linda knows her journey isn't over, but for now, she's happy watering her lavender and sipping tea by the window this time, after a full night's sleep.

Case 2 : James' Story: Wrenching Through the Pain and Finding a New Way Forward

James, 58, has always been a hands-on kind of guy. He runs a neighborhood auto shop that's been in his family for decades, and he takes pride in doing things the old-fashioned way—no shortcuts, no gimmicks, just good work [16,17]. But when his knee started giving out on him, even the simplest tasks became a grind. Climbing stairs felt like hauling a truck uphill, and crouching down to inspect a brake line? Forget it [16,17].

"Honestly, I thought I'd just pushed my body too hard over the years," he says. But when he finally went in for imaging, the news was clear and unwelcome. He had advanced osteoarthritis in his knee and early OA in his hip [16,17]. To make things worse, he had a history of gastric ulcers, so the usual anti-inflammatories were off the table. "No NSAIDs for me. Which felt like being handed a flat tire and told to keep driving [10,18]."

His doctors tried to work around it. He started getting steroid injections in the knee and hyaluronic acid in the hip. Sometimes, the relief was good enough to let him move freely for a week or two. But it didn't last [11,12]. "It was always up and down. I'd have a few decent days, and then the pain would come roaring back like I'd never treated it at all [11,12]."

That's when one of his specialists brought up something unexpected a clinical trial for IL-1Ra gene therapy. It was experimental, still in the research phase, and unlike anything James had ever considered [3,4]. "Gene therapy sounded like something out of sci-fi. I fix cars, not DNA," he jokes. "But when you're out of options, you start listening differently [3,4]."

He thought long and hard before enrolling. "I had doubts. I mean, who wouldn't? But I also didn't want

to keep patching things up. I needed something that might actually change the game [3,4]."

He received the therapy and was monitored closely, especially given his medical history. Slowly, something shifted. The pain that had ruled his days began to fade not overnight, but steadily [3]. He wasn't just managing; he was moving. Walking around the garage, picking up tools, even going for short hikes with his wife again [3,4].

"For the first time in a long time, I wasn't just waiting for the pain to come back. It felt stable. Like my body had finally found some footing [3,4]."

James knows what worked for him might not work for everyone. "What helped me wasn't just the treatment it was having a team that actually looked at the full picture. My joints, my stomach issues, my lifestyle. They didn't just hand me a script they found a path that made sense for me [7,24,25]."

Now, when customers drop by and complain about their knees creaking, James just grins and says, "There's hope, if you're willing to get a little experimental [3,4,24]."

VI. CONCLUSION

Although still fundamental, symptom-focused pharmacotherapies such as NSAIDs, paracetamol, SNRIs, and IA steroids/HA are restricted [9–12,18–20]. Newer DMOADs, like gene therapies, protease inhibitors, NLRP3 inhibitors, sprifermin, and NGF inhibitors, have the potential to improve symptoms and structure [1–7,13,22–24]. However, its integration into practice depends on addressing safety issues (such as RPOA), demonstrating long-term effectiveness, and focusing on patient subgroups that are responsive [14,22,24]. Digital outcome metrics, combination treatments, precision methods, and inclusive and well-designed trials are the future [7,24,25]. In resource-scarce nations like India, inexpensive treatments and scalable innovations must be given priority [16,17]. A humancentric approach and scientific rigor will be necessary to move from palliative care to genuine disease alteration [24,25].

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